Acute and Chronic Noncancer Inhalation Toxicity Factors for Acrylonitrile

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Abstract

Acrylonitrile (AN) is used extensively in the production of plastics, synthetic rubber, nitrile elastomers, resins, and acrylic fibers. The USEPA indicates that Texas contributes 11% of the nation's reported ambient AN emissions annually. Inhalation of AN vapors can cause respiratory irritation, and at higher levels, neurological symptoms including dizziness, weakness, headache, and impaired judgment. To ensure that the general public in Texas is protected against potential inhalation effects from AN exposure, the Texas Commission on Environmental Quality (TCEQ) has developed acute and chronic reference values (ReVs). An acute ReV (1-hr exposure duration) of 1,100 µg/m^3 was derived based on no signs or symptoms observed in human volunteers exposed to AN for up to 8 hours. A chronic ReV of 2.2 µg/m^3 was derived based on benchmark dose modeling for increased nasal lesions observed in female rats. The chronic ReV is comparable to the California EPA reference exposure level of 5 µg/m^3. Effects Screening Levels (ESLs) were calculated from ReVs by applying a target hazard quotient of 0.3, to account for possible cumulative exposure. ESLs are used to evaluate modeled ground level concentrations due to emissions from facilities during air permit reviews. The corresponding acute and chronic ESLs were 330 and 0.7 µg/m^3, respectively. Reproductive/developmental animal and epidemiological data were not used to derive ReVs since AN is not expected to be a developmental or reproductive toxicant in the absence of significant maternal toxicity. Furthermore, the overall carcinogenic weight-of-evidence shows that while AN is capable of causing tumors in rats and mice at high doses, AN does not appear to contribute to the development of cancerous tumors in humans. Thus, no inhalation unit risk factor was derived. The derived chronic ESL, however, is within the range of the concentrations at 1 x 10^{-5} cancer risk estimated by USEPA and thus, is expected to be protective against potential cancer risk.

Introduction

Acrylonitrile (AN) is a highly volatile, flammable, explosive, colorless liquid with a weakly sharp garlic-onion odor. AN is used in the production of plastics, synthetic rubber, nitrile elastomers, AN-butadiene-styrene and styrene-AN resins, and acrylic fibers, as well as an intermediate in the production of other important chemicals, such as adiponitrile and acrylamide (ATSDR 1990). According to the USEPA's Toxics Release Inventory (TRI), in 2007, approximately 7 million lbs of AN was released from 94 facilities, most of which (6.6 million lbs) was released by two facilities into on-site underground hazardous waste injection wells (EPA 2009). The USEPA's National Toxics Inventory (USEPA 2002) indicated that Texas contributed 11% of the annual AN nationwide ambient emissions (216,012 lbs of the nationwide 2,470,178 lbs). Measurable levels of atmospheric AN are associated with industrial sources. The median concentration of AN for 43 measurements near AN chemical plants in the U.S. was 2.1 µg/m^3 (ATSDR 1990).

Inhalation of AN vapors can cause respiratory irritation, and at higher levels, neurological symptoms including dizziness, weakness, headache, and impaired judgment (IARC 1999). To ensure that the general public in Texas is protected against the potential effects from AN exposure, the Texas Commission on Environmental Quality (TCEQ) has developed a series of inhalation toxicity factors e.g., ReVs and ESLs for effects evaluation using up-to-date toxicity information and *TCEQ Guidelines to Develop Toxicity Factors* (TCEQ 2012). ReVs, similar to USEPA's reference concentrations (RfCs) or California EPA's reference exposure levels (RELs), are used to evaluate air monitoring data. Health-based ESLs, calculated from ReVs by applying a policy-decision target hazard quotient (HQ) of 0.3, are used to evaluate predicted impacts for emissions from air permit facilities.

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Derivation of Acute ReVs and ESL

Respiratory Irritation and Neurological Effects

Headache, nausea, and dizziness have been reported in humans exposed to AN concentrations of 16-150 ppm for short periods (Wilson et al. 1948; Cole et al. 2008). The irritation and neurological effects of AN are considered most appropriate endpoints to derive an acute ReV. No signs or symptoms were reported in six male volunteer subjects following exposure up to 5 ppm for 8 hours (h) (Jakubowski et al. 1987). A free-standing no-observed-adverse-effect-level (NOAEL) of 10.8 mg/m^3 (5 ppm) for subjective symptoms was identified in the Jakubowski et al. (1987) study and was used as the point of departure (POD) to derive the acute ReV and ESL. The NOAEL is supported by a report of occupational exposure which indicates that exposure to AN at 10 ppm or less was without effects while exposure to 12-15 ppm in occupational workers produced mild irritation and headache regardless of exposure duration (AEGL 2007). Additionally, acute inhalation exposure studies in several laboratory animal species showed that AN exposure induced effects similar to those observed in humans (Dudley and Neal 1942). The NOAELs as well as the lowest-observed-adverse-effect-levels (LOAELs) identified from animal studies are higher than those from human studies and thus, were not used as the POD to derive acute toxicity values.

The precise mode of action (MOA) of the acute toxic response is not fully elucidated, but may involve the binding of AN or 2-cyanoethylene oxide (CEO). The primary route of AN metabolism to form the key toxic metabolite is by oxidation of AN to CEO. This intermediate may undergo further metabolism by either epoxide hydrolase or conjugation to glutathione to form cyanide (CN^{-1}). The acute effects (e.g., irritation of the respiratory tract) of AN appear to be largely due to CN^{-1} (Kedderis et al. 1996). AN-induced neurological effects in laboratory animals appear to involve the parent compound and the CN^{-1} (AEGL 2007).

Reproductive/Developmental Toxicity Studies

The reproductive and developmental toxicities of AN have been well studied in animals and humans. Cross-sectional epidemiological studies of reproductive outcomes in Chinese AN-exposed workers found an increased prevalence of adverse reproductive outcomes associated with average workplace air concentrations of 3.6 ppm and 7.5 ppm (USEPA 2011). Adverse outcomes with statistically significantly increased prevalence compared with unexposed workers included premature deliveries, stillbirths, sterility, birth defects, and pregnancy complications. However, in a weight-of-evidence (WOE) review, Neal et al. (2009) indicated that the data were deemed insufficient to establish causation (e.g., potential confounding factors or lack of exposure data). Epidemiological studies do not demonstrate causality and are not sufficiently robust to be used for risk assessment. While fetotoxicity and malformations at maternally toxic levels were observed in rodent developmental studies, the existing animal inhalation studies (e.g., Saillenfait et al. 1993, Murray et al. 1978, Nemec et al. 2008) do not show any clear indication of decreased in fertility, dominant lethal, reproductive or teratogenic effects of AN exposure at doses below those producing parental toxicity. AN is not expected to be a developmental or reproductive toxicant in the absence of significant maternal toxicity. Thus, the existing animal and epidemiological data were not used to derive toxicity values for reproductive/developmental effects.

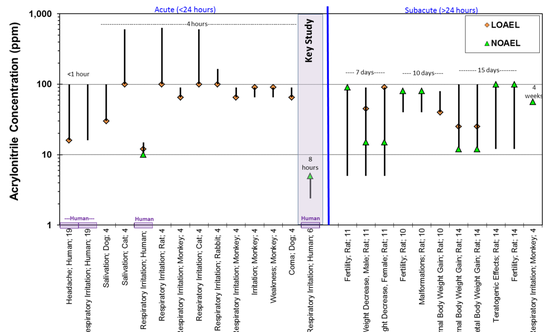
POD for the Key Study and Critical Effects

The NOAEL of 5 ppm identified from the Jakubowski et al. (1987) study was used as the POD to derive the acute ReV and ESL for AN. Since the Jakubowski et al. (1987) study provides only a free-standing NOAEL; there is no documented critical effect in this study. However, symptoms observed in workers (exposed to 16-100 ppm AN for 20-45 min) such as irritation of mucous membranes and headache from the Wilson et al. (1948) occupational study may be considered critical effects for acute AN exposure. The POD was adjusted for exposure duration to calculate the POD Human Equivalent Concentration (POD_{HEC}). Appropriate UFs were then applied to derive the acute Rev and ESL. As shown in Table 1, the derived acute ReV of 100 µg/m^3 (500 ppb) is used for the evaluation of ambient air monitoring data and acute ESL of 330 µg/m^3 (150 ppb) is used for air permit reviews. Overall, the quality of the database and key study are considered medium; however, the confidence in the acute database is medium to high. Confidence in the derived ReV is medium as the chosen POD was based on a free-standing NOAEL.

Table 1. Derivation of the Acute ReV and ESL for AN

Key Study	**Jakubowski et al. (1987)**
Study Population	Six male volunteers (aged 28-45)
Exposure Method	Inhalation of either 2.4 or 5 ppm exposure
Exposure Duration	8 h
Critical Effects	Absence of signs or symptoms in human volunteers; headache, nasal and ocular irritation would be expected at ≥ 16 ppm
NOAEL (= POD)	5 ppm (free-standing NOAEL)
Extrapolation to 1 h (POD_{ADJ})	5 ppm (8-h free-standing POD was not adjusted to 1-h exposure duration)
POD_{HEC}	5 ppm
Total UFs	10
Interspecies UF_A	1
Intraspecies UF_H	10
Incomplete Database UF_D	1
Acute ReV [1 h] (HQ = 1)	1,100 µg/m3 (500 ppb)
Acute ESL [1 h] (HQ = 0.3)	330 µg/m3 (150 ppb)[a]

Figure 1. Exposure-Response Array for Acute and Subacute Exposure to Acrylonitrile



Derivation of Chronic ReVs and ESL

Local irritation, neurological, hematological, survival, reproductive, and systemic effects have been observed in chronic inhalation toxicity studies with AN. Nasal irritation is the most sensitive endpoint seen in chronic inhalation studies of rats. There are two well-conducted rat studies on nasal irritation by Nemec et al. (2008) and Quast et al. (1980) available. Both studies administered multiple exposure levels and showed dose-effect relations. Both the Nemec et al. (2008) and the Quast et al. (1980) studies were used as key studies to develop the chronic ReV and ESL. The Quast et al. (1980) study was also used by the California EPA Office of Environmental Health Hazard Assessment (OEHHA 2001) and USEPA (1991) to derive their chronic noncancer toxicity values. While USEPA (2011) used the Lu et al. (2005) epidemiological study as key study for its new RfC for neurological effects, because of potential limitations of this study as noted by Lu et al. (2005) and USEPA (2011), the TCEQ determined to not use the Lu et al. (2005) study or other epidemiological studies to develop the chronic ReV and ESL.

Nemec et al. (2008) Study

Nemec et al. (2008) conducted a two-generation reproductive toxicity inhalation study in SD rats. Groups of rats (F_0 generation, 25 rats/sex/group) were exposed to AN via whole body inhalation at 0, 5, 15, 45, and 90 ppm for 6 h/d, 7 d/week for 10 weeks prebreeding exposure; these animals were randomly bred to produce an F_1 generation. Histopathologic changes in nasal tissues were observed in F_0 males and females at 45 ppm, F_1 males at 5, 15, and 45 ppm, and F_1 females in the 15 and 45 ppm exposure groups. A NOAEL and LOAEL of 5 and 15 ppm, respectively, for nasal lesions in the F_1 rats were identified from this study. The lesions showed a clear exposure-related response in incidence and severity for all endpoints examined in F_1 males and for hyperplasia in respiratory/transitional epithelium examined in F_1 female rats. The incidence data from both F_1 males and females for hyperplasia in respiratory/transitional epithelium (the most sensitive endpoint) were then pooled for benchmark concentration (BMC) modeling.

Quast et al. (1980) Study

Quast et al. (1980) exposed groups of SD rats (100 rats/sex/group) to AN via inhalation at 0, 20, and 80 ppm for 6 h/d, 5 d/week, for two years. Results of this study showed long-term exposure of AN to rats induced statistically significant dose-response degenerative and inflammatory changes in the respiratory epithelium of the nasal tissue. A LOAEL of 20 ppm for nasal irritation was identified from this study. BMC modeling was conducted for incidence data for endpoints examined either in either males or females which showed dose-response increase tissue damage.

POD for Key Studies and Critical Effect(s)

BMC modeling using USEPA BMD software (version 2.2) for data reported from the Nemec et al. (2008) and Quast et al. (1980) key studies was conducted. The BMC modeling results were summarized in Table 2. The $BMCL_{10}$ of 0.564 ppm based on the incidence data for flattening of the respiratory epithelium of the nasal turbinates in female rats (Quast et al. 1980) has the lowest $BMCL_{10}$ and was used as the POD to derive chronic ReV and ESL. The nasal lesions is considered a critical effect. The POD was adjusted for exposure duration and a rat-to-human adjustment was applied to calculate the POD_{HEC}. Appropriate UFs were then applied to derive the chronic Rev and ESL. As shown in Table 3, the derived chronic ReV of 1 ppb (2.2 µg/m^3) is used for the evaluation of ambient air monitoring data; and the ESL of 0.3 ppb (0.7 µg/m^3) is used for air permit reviews. Overall, the quality of two key studies and confidence in the database are high. Confidence in the derived chronic ReV is also high as the dose-response BMC modeling was conducted. While no unit risk factor is derived by TCEQ, the derived chronic ESL of 0.7 µg/m^3 is within the range of the concentrations (0.32 µg/m^3) at 1 x 10^{-5} cancer risk estimated by USEPA (2011). The derived chronic ESL is expected to be protective against potential cancer risk.

Table 2. Summary of BMC Modeling Results Based on Incidence Data of Endpoints Examined

Endpoint examined	**Best-fitting Model**	**AIC**	**χ^2 P-value**	**Scaled residuals**	**BMC_{10}**	**$BMCL_{10}$**
Nemec et al. 2008 Study						
Hyperplasia in respiratory and transitional epithelium in pooled F_1 male and female rats	Multistage, Weibull, Quantal	69.16	0.2443	< |2|	1.295	0.919
Quast et al. 1980 Study						
Hyperplasia in the nasal turbinates in male rats	Weibull	19.28	0.994	< |2|	12.134	2.961
Hyperplasia of mucus-secreting cells in male rats	Log-Logistic	28.42	0.9429	< |2|	1.778	0.777
Focal inflammation in the nasal turbinates in female rats	Log-Probit	40.75	0.4185	< |2|	3.472	1.247
Flattening of the respiratory epithelium of the nasal turbinates in female rats	Log-Logistic	28.42	0.9429	< |2|	1.533	0.564

Table 3. Derivation of the Chronic ReV and ESL for AN

Key Study	**Quast et al. (1980) chronic study**
Study Population	100 SD female rats per exposure group
Exposure Method	Via inhalation at 0, 20, and 80 ppm
Exposure duration	6 h/d, 5 d/week, for 2 years
Critical Effects	Flattening of the respiratory epithelium of the nasal turbinates in females
NOAEL	Not available
LOAEL	20 ppm
POD	0.564 ppm ($BMCL_{10}$)
Extrapolation to continuous exposure (POD_{ADJ})	0.1 ppm
POD_{HEC}	0.0291ppm (AN is considered a Category 1 gas (local irritation) and the default dosimetric adjustment from rat-to-human exposure is conducted. The POD_{HEC} is calculated by multiplying the regional gas dose ratio for the extrathoracic region ($RGDR_{ET}$) to POD_{ADJ}
Total UFs	30
Interspecies UF_A	3
Intraspecies UF_H	10
LOAEL to NOAEL UF_L	Not applicable (BMC modeling was conducted)
Incomplete Database UFD	1
Chronic ReV (HQ = 1)	2.2 µg/m^3 (1 ppb)
Chronic ESL (HQ = 0.3)	0.7 µg/m^3 (0.3 ppb)

Table 4. Comparison of Various Chronic Toxicity Values

Table 4 below shows that the derived chronic ReV is in agreement with the chronic toxicity values derived by USEPA and California EPA.

	Chronic Toxicity Value	**$POD_{[HEC]}$**	**Key Study**
ReV (TCEQ)	2.2 µg/m^3 (1 ppb)	0.063 mg/m^3 (0.029 ppm) ($BMCL_{10}$)	Quast et al. 1980
RfC (USEPA 1991)	2 µg/m^3 (0.9 ppb)	1.9 mg/m^3 (0.88 ppm) ($NOAEL_{[HEC]}$)	Quast et al. 1980
RfC (USEPA 2011)	3 µg/m^3 for male rats (1.4 ppb)	0.082 mg/m^3 (0.038 ppm) ($BMCL_{10}$)	Quast et al. 1980
	2 µg/m^3 for female rats (0.9 ppb)	0.059 mg/m^3 (0.027 ppm) ($BMCL_{10}$)	
RfC (USEPA 2011)	0.9 µg/m^3 (0.4 ppb)	0.0086 mg/m^3 (0.004 ppm) ($NOAEL_{[HEC]}$)	Lu et al. 2005
REL (OEHHA 2001)	5 µg/m^3 (2.3 ppb)	1.5 ppm (3.225 mg/m^3) (BMC_{05})	Quast et al. 1980

[a] Based on the acute ReV of 1,100 µg/m^3 (500 ppb) multiplied by a target hazard quotient (HQ) of 0.3 to account for cumulative and aggregate risk during the air permit review.

Figure 2. Exposure-Response Array for Chronic Exposure to Acrylonitrile